Integrated Impact Assessment Report for Clinical Commissioning Policies

Policy Reference Number	F02X04		
Policy Title	Immune Tolerance Induction (ITI) for haemophilia A (all ages)		
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Section K - Activity Impact			
Theme	**Questions**	**Comments** (Include source of information and details of assumptions made and any issues with the data)	
K1 Current Patient Population & Demography / Growth	K 1.1 What is the prevalence of the disease/condition?	K1.1 This proposed policy formalises the existing position that immune tolerance induction (ITI) will be **routinely commissioned for children** with severe haemophilia A and a factor VIII inhibitor.[i] ITI will **not be routinely commissioned for adults** with the same condition. An estimated 605 children in England suffer from severe haemophilia A in 2014/15.[ii] Moreover, an estimated 1,100 adults in England are living with severe haemophilia A in 2014/15.[iii] This corresponds to a **prevalence rate** of around 5 per 100,000 amongst children and c. 3 per 100,000 amongst adults in England.[iv]	

		Haemophilia A occurs in one in every 5,000 male births worldwide,[v] and the **incidence** in England of severe haemophilia A in children is estimated in the region of 59 per year in 2014/15, and fewer than 10 per year in adults in 2014/15.[vi] Note that ITI is intended only for a subset of children with severe haemophilia A who have a Factor VIII inhibitor.
	K1.2 What is the number of patients currently eligible for the treatment under the proposed policy?	K1.2 This policy is intended for a minority of patients with severe haemophilia A that form antibodies (inhibitors) against administered factor VIII (FVIII). Around 25%-30% of **children** with severe haemophilia A form inhibitors against administered factor VIII after commencing treatment.[vii] Based on this, the incidence of severe haemophilia A patients aged 18 and under in England who develop inhibitors is likely to be around 15 to 18 in 2014/15.[viii] Similarly, the incidence of **adults** with severe haemophilia A with inhibitors in England is estimated at around 2 patients per year.[ix]
	K1.3 What age group is the treatment indicated for?	K1.3 The treatment is indicated for all ages; however the position is to routinely commission treatment for children (age 18 and below), but not routinely commission the treatment for adults.

	K1.4 Describe the age distribution of the patient population taking up treatment?	K1.4 Severe haemophilia A is usually diagnosed at a very young age[x] and most patients undergoing ITI are expected to be between 12 and 18 months old.[xi] Moreover, severe haemophilia A primarily affects males[xii] and ITI is therefore expected to be offered to male patients predominantly.
	K1.5 What is the current activity associated with currently routinely commissioned care for this group?	K1.5 All of the eligible **children** identified in K1.2 are estimated to undergo **ITI** as the treatment is routinely commissioned.[xiii] Therefore, current annual activity is in the range of 15-18 patients who receive an estimated 6.6m to 15.8m units of recombinant factor VIII concentrate for ITI (based on an average length of treatment of 16 months).[xiv] If bleeds occur **during ITI**, these are typically treated using **bypassing agents**.[xv] Patients may also receive prophylaxis with bypassing agents.[xvi] For an average of 12 months after ITI, patients would subsequently be tapered off the high doses of FVIII. During this time, patients gradually receive lower doses until they reach the levels of the peer group of those without inhibitors.[xvii] After ITI, the median units per patient per year of **factor VIII** is estimated at around 100,000 to 200,000 units (under age 18).[xviii] If a patient were to fail treatment, they would continue use with bypassing agents. **Adults** with inhibitors typically require **bypassing agents**[xix] to treat bleeds. The frequency and dosage however varies significantly among patients.[xx] For patients that have inhibitors, they may use

		prophylactic by-passing agents.[xxi]
	K1.6 What is the projected growth of the disease/condition prevalence (prior to applying the new policy) in 2, 5, and 10 years?	K1.6 Historic data on prevalence for severe haemophilia A may not be reliable to estimate future growth because of changes in the prevalence of haemophilia patients with HIV and hepatitis.[xxii] Demographic growth of the male population aged 0-19 years is therefore used to estimate future **prevalence for children.** The compound annualised growth rate (CAGR) of this population between 2015/16 and 2020/21 is c. 0.6%. Future prevalence is therefore estimated in the region of: [xxiii] • 610 in 2016/17 • 610 in 2017/18 • 625 in 2020/21 The compound annual growth rate in the number of registrations for **children** with severe haemophilia A registered in the UKHCD registry between 2008/09 and 2013/14 was c. 2.6% p.a.[xxiv] If historic trends continue, future **incidence of the target population** is estimated in the region of: [xxv] • 15 to 19 in 2016/17 • 16 to 19 in 2017/18 • 17 to 21 in 2020/21 Similarly, for the **adult** population, the **prevalence** is estimated in the

		region of:[xxvi] • 1,115 in 2016/17 • 1,125 in 2017/18 • 1,150 in 2020/21 The **incident** population of those with inhibitors is estimated to relate to new migrants to the UK.[xxvii] As there is only a very small number of patients affected each year, the number of adults is assumed to stay at current levels of c. 2 per year until 2020/21. [xxviii]
	K1.7 What is the associated projected growth in activity (prior to applying the new policy) in 2,5 and 10 years	K1.7 Based on the future number of **children** affected as described in K1.6, total units of recombinant factor VIII concentrate for ITI is estimated in the range of:[xxix] • 6.9m to 16.6m units in 2016/17 • 7.1m to 17.0m units in 2017/18 • 7.7m to 18.4m units in 2020/21 The usage of FVIII after successful ITI is estimated to stay as described in K1.5 for both **children** and **adults**.
	K1.8 How is the population currently distributed geographically?	K1.8 Across England. The centres with the most number of severe haemophilia A patients in 2013/14 were in London, Thames Valley & Essex, West Midlands, North West and Yorkshire and Humber commissioning regions.[xxx]

K2 Future Patient Population & Demography	K2.1 Does the new policy: move to a non-routine commissioning position / substitute a currently routinely commissioned treatment / expand or restrict an existing treatment threshold / add an additional line / stage of treatment / other?	K2.1 This policy formalises the position to routinely commission ITI in children with severe haemophilia A and inhibitors of factor VIII. ITI will not be routinely commissioned for adults with severe haemophilia A and inhibitors of factor VIII. ITI is currently routinely commissioned for children and not routinely undertaken for adults (however, there is no commissioning policy in place currently).
	K2.2 Please describe any factors likely to affect growth in the patient population for this intervention (e.g. increased disease prevalence, increased survival)	K2.2 Changes in birth rates could affect future prevalence of those requiring ITI under the routinely commissioned policy as this treatment is taken up by children aged 18 months and below (as set out in K1.4). The prevalence of the target population of adults could be affected by migration rates, survival, or co-morbidities of the incident population (HIV, hepatitis).
	K 2.3 Are there likely to be changes in geography/demography of the patient population and would this impact on activity/outcomes? If yes, provide details	K2.3 Haemophilia is caused by an inherited genetic mutation[xxxi] and no changes in geography/demography could be identified.
	K2.4 What is the resulting expected net increase or decrease in the number of patients who will access the treatment per year in year 2, 5 and 10?	K2.4 No changes in the number of patients taking up treatment relative to the 'do nothing' scenario are anticipated under the policy.[xxxii] The number of patients accessing treatment per year is as described in K1.7. For **children** there is no change because they are already receiving the treatment. For **adults**, there is no change because currently these patients would not be receiving treatment. The number of patients who fall

		outside of the cohort covered by the proposed policy, or for whom exceptionality might be demonstrated is likely to be very small.
K3 Activity	K3.1 What is the current annual activity for the target population covered under the new policy? Please provide details in accompanying excel sheet	K3.1 Current activity is as described in K1.5; children with inhibitors would be receiving ITI, and adults would not.
	K3.2 What will be the new activity should the new / revised policy be implemented in the target population? Please provide details in accompanying excel sheet	K3.2 The majority of centres providing ITI are already following the proposed treatment regimen (as described in the policy proposition) and the effect on activity of the policy would be minimal.[xxxiii] As such, no material changes relative to the 'do-nothing' are anticipated and the new activity would be as described in K1.7.
	K3.3 What will be the comparative activity for the 'Next Best Alternative' or 'Do Nothing' comparator if policy is not adopted? Please details in accompanying excel sheet	K3.3 The 'do nothing' activity is as described in K1.7, and is similar to the 'policy' treatment.
K4 Existing Patient Pathway	K4.1 If there is a relevant currently routinely commissioned treatment, what is the current patient pathway? Describe or include a figure to outline associated activity	K4.1 Infants and children with severe haemophilia tested for an inhibitor at least every third exposure day (ED) until 20 EDs and subsequently every 3-6 months until 150 EDs to ensure that an inhibitor is detected and treated early. When an inhibitor is detected all cases should be offered immune tolerance induction (ITI) in order to optimise the chances of inhibitor eradication. ITI should be started as soon as an inhibitor is confirmed irrespective of the titre. First line ITI should be conducted using recombinant FVIII

		concentrate (unless as part of a clinical trial). This is usually with the product used by the patient at the time of inhibitor development. For children, treatment undertaken in line with the UKHCDO protocol which reflects the UK clinical consensus on the optimal ITI treatment regime for children under the age of 18 Where there is an inadequate sustained downward trend in the inhibitor titre, the specialist team would be expected to consider alternative strategies.
	K4.2. What are the current treatment access criteria?	K4.2 NHS England will routinely commission ITI for the eradication of factor VIII inhibitors where the patient: i. Is aged <19 years of age and has severe haemophilia A AND ii. Has a factor VIII inhibitor confirmed on more than one occasion by a Nijmegen-modified Bethesda assay, that compromises the effect of prophylaxis or treatment of bleeds at standard doses of FVIII AND iii. in the rare cases where a young adult patient previously treatment naive develops inhibitors soon after exposure to exogenous Factor VIII
	K4.3 What are the current treatment stopping points?	K4.3 Stopping criteria for good responders (75% of patients): Patients continue on ITI with monitoring to detect the peak inhibitor titre and the downward trend in level. When the titre becomes negative the dose tapering schedule should be followed. The ITI is considered successful once the patient is on prophylaxis doses (≤50U/kg alternate days) with a FVIII level of ≥ 1 iu/dl.

		Stopping criteria for poor responders (25% of patients): If there is no sustained downward trend after 6 months of first line ITI, escalate to full dose (200 IU/kg/day). If there is no sustained downward trend after 6 months of full dose ITI (200 IU/kg/day), change to pd FVIII and / or immunosuppression for a further 6 months. If there is no sustained downward trend after 6 months of pd FVIII and immunosuppression and FVIII cannot be used to prevent and treat bleeds ITI should be stopped. (N.B. time periods indicate maximum time to wait before evaluation of response. Earlier changes can be made if the inhibitor titre is increasing or a sustained downward trend is unlikely).
K5 Comparator (next best alternative treatment) Patient Pathway	K5.1 If there is a 'next best' alternative routinely commissioned treatment what is the current patient pathway? Describe or include a figure to outline associated activity. K5.2 Where there are different stopping points on the pathway please indicate how many patients out of the number starting the pathway would be expected to finish at each point (e.g. expected number dropping out due to side effects of drug, or number who don't continue to treatment after having test to determine likely success). If possible please indicate likely outcome for patient at	K5.1 ITI is the only 'cure' for inhibitors but as it sometimes takes a while to work (it can take over one year), bypassing agents can be used to treat bleeds or as prophylaxis. K5.2 Not applicable.

	each stopping point.	
K6 New Patient Pathway	K6.1 Describe or include a figure to outline associated activity with the patient pathway for the proposed new policy K6.2 Where there are different stopping points on the pathway please indicate how many patients out of the number starting the pathway would be expected to finish at each point (e.g. expected number dropping out due to side effects of drug, or number who don't continue to treatment after having test to determine likely success). If possible please indicate likely outcome for patient at each stopping point.	K6.1 and K6.2 The patient pathway and stopping points would be the same under the proposed new policy (in line with the UKHCDO protocol). See K4
K7 Treatment Setting	K7.1 How is this treatment delivered to the patient? o Acute Trust: Inpatient/Daycase/ Outpatient o Mental Health Provider: Inpatient /Outpatient o Community setting o Homecare delivery K7.2 Is there likely to be a change in	K7.1 The treatment would typically be delivered through homecare. Most patients will have a venous access device inserted.[xxxiv] K7.2 No change anticipated in delivery setting or capacity

	delivery setting or capacity requirements, if so what? *e.g. service capacity*	requirements.
K8 Coding	K8.1 In which datasets (e.g. SUS/central data collections etc.) will activity related to the new patient pathway be recorded?	K8.1 Activity will be recorded in the United Kingdom Haemophilia Centres Doctors' Organisation (UKHCDO) National Haemophilia Database.
	K8.2 How will this activity related to the new patient pathway be identified?(e.g. ICD10 codes/procedure codes)	K8.2 Activity can be directly identified within the UKHCDO National Haemophilia Database.
K9 Monitoring	K9.1 Do any new or revised requirements need to be included in the NHS Standard Contract Information Schedule?	K9.1 Yes as changes are being made to the policy.
	K9.2 If this treatment is a drug, what pharmacy monitoring is required?	K9.2 No pharmacy monitoring is required.
	K9.3 What analytical information /monitoring/ reporting is required?	K9.3 Analytical monitoring is carried out in the laboratory.
	K9.4 What contract monitoring is required by supplier managers? What changes need to be in place?	K9.4 Contract monitoring is managed by the Commissioning Support Unit (CSU) and the necessary information is then shared with supplier managers (commissioners).

	K9.5 Is there inked information required to complete quality dashboards and if so is it being incorporated into routine performance monitoring?	K9.5 ITI is excluded from the quality dashboard.
	K9.6 Are there any directly applicable NICE quality standards that need to be monitored in association with the new policy?	K9.6 No.
	K9.7 Do you anticipate using Blueteq or other equivalent system to guide access to treatment? If so, please outline. *See also linked question in M1 below*	K9.7 The use of a prior approval software platform would be explored and would be linked to the UKHCDO National Haemophilia Database.
Section L - Service Impact		
Theme	**Questions**	**Comments** (Include source of information and details of assumptions made and any issues with the data)
L1 Service Organisation	L1.1 How is this service currently organised? (i.e. tertiary centres, networked provision)	L1.1 The service is currently delivered by children's hospitals with haemophilia comprehensive care centres.
	L1.2 How will the proposed policy change the way the commissioned service is organised?	L1.2 No change is organisation in anticipated.
L2 Geography & Access	L2.1 Where do current referrals come from?	L2.1 Referrals for haemophilia will initially come through primary care or from secondary paediatric services, or through obstetric units.

	L2.2 Will the new policy change / restrict / expand the sources of referral?	L2.2 The policy will not change the sources of referral.
	L2.3 Is the new policy likely to improve equity of access	L2.3 The policy will result in an improvement in the equity of access as the treatment would be standardised.
	L2.4 Is the new policy likely to improve equality of access / outcomes?	L2.4 The policy will result in an improvement in the equality of access as the treatment would be standardised.
L3 Implementation	L3.1 Is there a lead in time required prior to implementation and if so when could implementation be achieved if the policy is agreed?	L3.1 No lead in time required.
	L3.2 Is there a change in provider physical infrastructure required?	L3.2 No change in provider physical infrastructure required.
	L3.3 Is there a change in provider staffing required?	L3.3 No change in provider staffing required.
	L3.4 Are there new clinical dependency / adjacency requirements that would need to be in place?	L3.4 No

	L3.5 Are there changes in the support services that need to be in place?	L3.5 Changes in support services will not be required.
	L3.6 Is there a change in provider / inter-provider governance required? (e.g. ODN arrangements / prime contractor)	L3.6 No
	L3.7 Is there likely to be either an increase or decrease in the number of commissioned providers?	L3.7 No change in the number of commissioned providers is anticipated.
	L3.8 How will the revised provision be secured by NHS England as the responsible commissioner? (e.g. publication and notification of new policy, competitive selection process to secure revised provider configuration)	L3.8 Stakeholders to be informed regarding changes.
L4 Collaborative Commissioning	L4.1 Is this service currently subject to or planned for collaborative commissioning arrangements? (e.g. future CCG lead, devolved commissioning arrangements)?	L4.1 No plans at present.
Section M - Finance Impact		
Theme	**Questions**	**Comments** (Include source of information and details of assumptions made and any issues with the data)
M1 Tariff	M1.1 Is this treatment paid under a	M1.1 No (see M1.2).

	national prices*, and if so which?	
	M1.2 Is this treatment excluded from national prices	M1.2 Factor VIII is excluded from national tariff as a high cost drug.
	M1.3 Is this covered under a local price arrangements (if so state range), and if so are you confident that the costs are not also attributable to other clinical services?	M1.3 Based on the Dictionary of Medicines, the price of factor VIII used for ITI is £126 to £178 per 250 units and vial (exclusive of VAT).[xxxv] The average cost per patient per year is set out in M2.1
	M1.4 If a new price has been proposed how has this been derived / tested? How will we ensure that associated activity is not additionally / double charged through existing routes	M1.4 Not applicable.
	M1.5 is VAT payable (Y/N) and if so has it been included in the costings?	M1.5 In cases where homecare is used (estimated to be the majority of patients[xxxvi]), VAT may be recoverable.[xxxvii]
	M1.6 Do you envisage a prior approval / funding authorisation being required to support implementation of the new policy?	M1.6 No.
M2 Average Cost per Patient	M2.1 What is the revenue cost per	M2.1 The revenue costs per patient for **children** receiving **ITI** treatment in year 1 could be in the region of £300,000 (range

	patient in year 1?	between £200,000 and £400,000).[xxxviii] In addition to the cost of the drug, there would be costs in relation to equipment to administer ITI, as well as in relation to delivery of the drug via homecare. These costs are however minimal in comparison the cost of the treatment itself. [xxxix]
	M2.2 What is the revenue cost per patient in future years (including follow up)?	M2.2 **Children** will receive treatment of **ITI** for an average of 16 months.[xl] Therefore, 4 months of ITI in year 2 have an estimated cost of c. £100,000 (range: £70,000 to £140,000) per patient.[xli] There is an additional tapering phase for an estimated average of 12 months after treatment. The average cost per patient during this phase is estimated in the region of £130,000 to £260,000.[xlii] After successful completion of ITI, patients could receive prophylactic treatment with factor VIII, which could cost in the region of £22k to £109k for a young child and increase to £175k to £491k in adulthood.[xliii] **Without successful ITI** the cost of a prophylactic bypassing agents could be in the region of c. £70k to £561k for a young child and increase to c. £561k to £2.5m in adulthood.[xliv] Any bleeds that occur following successful ITI will be treated with factor VIII instead of a bypassing agent.
M3 Overall Cost Impact of this Policy to NHS England	M3.1 Indicate whether this is cost saving, neutral, or cost pressure to NHS England	M3.1 Cost neutral as there is no material change to the 'do-nothing' as this treatment is already being commissioned in children (as described in K3.2).
	M3.2 Where this has not been identified, set out the reasons why this cannot be measured	M3.2 Not applicable.

M4 Overall cost impact of this policy to the NHS as a whole	M4.1 Indicate whether this is cost saving, neutral, or cost saving for other parts of the NHS (e.g. providers, CCGs)	M4.1 Cost neutral as described in M3.1.
	M4.2 Indicate whether this is cost saving, neutral, or cost pressure to the NHS as a whole	M4.2 Cost neutral as described in M3.1.
	M4.3 Where this has not been identified, set out the reasons why this cannot be measured	M4.3 Not applicable.
	M4.4 Are there likely to be any costs or savings for non NHS commissioners / public sector funders?	M4.4 None identified.
M5 Funding	M5.1 Where a cost pressure is indicated, state known source of funds for investment, where identified *e.g. decommissioning less clinically or cost-effective services*	M5.1 Not applicable.
M6 Financial Risks Associated with Implementing this Policy	M6.1 What are the material financial risks to implementing this policy?	M6.1 The number of children accessing the treatment and the level of FVIII required for ITI per child could increase the cost.
	M6.2 Can these be mitigated, if so how?	M6.2 Note identified.

	M6.3 What scenarios (differential assumptions) have been explicitly tested to generate best case, worst case and most likely total cost scenarios?	M6.3 There is some uncertainty and variation around the number of patients taking up treatment each year and the dosage of FVIII such patients would receive. The 'low' case assumes that patients have an average weight of 10kg. The 'mid' case uses 15kg as an average patient weight. The 'high' scenario assumes an average weight per patient 20kg. Throughout, an average cost per 250 units of FVIII of c. £150 is assumed and the pathway is as described in endnote xivxiv.
M7 Value for Money	M7.1 What evidence is available that the treatment is cost effective? *e.g. NICE appraisal, clinical trials or peer reviewed literature*	M7.1 No recent cost-effectiveness studies found.
	M7.2 What issues or risks are associated with this assessment? *e.g. quality or availability of evidence*	M7.2 Not applicable.
M8 Cost Profile	M8.1 Are there non-recurrent capital or revenue costs associated with this policy? *e.g. Transitional costs, periodical costs*	M8.1 No.
	M8.2 If so, confirm the source of funds to meet these costs	M8.2 Not applicable.

[i] See policy proposition for definition of Severe Haemophilia and factor VIII.

[ii] This is based on 709 registered patients with severe haemophilia a (aged under 18) in 2013/14 in the UKHCDO register [Source: UKHCDO. UK National Haemophilia Database Bleeding Disorder Statistics for 2013-2014]. This number is grown by the growth of the male children to arrive at 2014/15 (based on Office for National Statistics (ONS) (2012). Population Projections). The resulting figure is then reduced to cover only the population of England (84% of the UK population) [Based on Office for National Statistics (ONS) (2015). Population Estimates for UK, England and Wales, Scotland and Northern Ireland, Mid-2014]. Figures rounded.

[iii] Based in 1,293 registered patients in 2013/14 [Source: UKHCDO register]. Corrected as described in endnote ii and grown by the growth rate of the population aged 18 and above arrive at 2014/15 figures for England (based on ONS (2012). Population Projections).

[iv] Based on ONS (2015). Population Estimates for UK, England and Wales, Scotland and Northern Ireland, Mid-2014 for children (aged 0-18) and adults (aged 19 and above)

[v] NHS Choices.

[vi] This is based on 63 newly registered patients under the age of 19 in 2013/14 in the UKHCD register, grown by the average yearly growth rate in new registrations since 2008/09 and corrected to cover only the population of England (as in endnote ii). Adult registrations of 10 per year in the UK were similarly corrected and grown by the growth in net migration to England (based on ONS (2012). Population Projections). This could relate to patients that have migrated to England. (based on discussions with the policy working group).

[vii] Based on the policy document, discussions with the policy working group and Collins, PW, et.al. (2014). "Factor VIII brand and the incidence of factor VIII inhibitors in previously untreated UK children with severe hemophilia A, 2000-2011". *Blood*. 124(23): 3389–3397.

[viii] Based on 63 reported new registrations of severe haemophilia A under the age of 19 in 2013/14 [Source: UKHCDO register]. This number is corrected to cover only the population in England and is grown in line with the average growth rate in patients registered within the UKHCD dataset since 2008/09 to arrive at 2014/15 figures [based on ONS (2015) Population Estimates]. This leads to an estimated 59 cases in England of which 25%-30% are expected to develop a FVIII inhibitor. Figures are rounded, the unrounded figures are used in the calculations that follow.

[ix] This is based on under 10 new cases of severe haemophilia A of which 25%-30% would develop an inhibitor to administered factor VIII. This number includes those patients that have migrated to England or those who develop a more severe form of haemophilia A.

[x] Based on discussions with the policy working group, registrations data as reported in UKHCDO Register for 2013/14. Moreover, in the United States (used as a proxy for England), median age at diagnosis of those with severe haemophilia is 1 month [Source: Centers for Disease Control and Prevention. Hemophilia – Data & Statistics. [Online] Available from http://www.cdc.gov/ncbddd/hemophilia/data.html [Accessed: 19/11/2015]], another study reports the mean age of diagnosis at 3.7 months among 20 patients [Source: H. Pollmann et. al (2010). “When is severe haemophilia A diagnosed in children and when do they start to bleed?” *Hamostaseologie*.Vol 30.]

[xi] Based in discussions with the policy working group.

[xii] For instance, in 2012/13 out of 689 registered children with severe haemophilia A, 686 were male with 3 female carriers. [Source: UKHCDO. UK National Haemophilia Database Bleeding Disorder Statistics for 2012-2013].

[xiii] Based on discussions with the policy working group.

[xiv] Based on discussions with the policy working group. The number of units is based on an average weight per patient of 10 kg to 20 kg and a treatment period of 16 months. Moreover, a stylised patient pathway assumes [‘Pathway’ based on: UKHCDO protocol for first line immune tolerance induction for children with severe haemophilia A: A protocol from the UKHCDO Inhibitor and Paediatric Working Parties (18th November 2015)]:

As a high level estimate, 50% of patients receive 50 units per kg of body weight every second day in the first month, of which 25% will increase the dosage to 100 units/kg daily in the remaining months; 45% of patients start off with a dose 100 units/kg daily of which 40% will increase to 200 units/kg daily after the first month; the remaining 5% of patients are assumed to receive 200 units/kg per day for the whole treatment period. The number of units stated in the text combines the volume usage of new patients receiving ITI and the proportionate usage of patients in their second year of ITI (i.e. those on the remaining 4 months of treatment). Estimates of these percentages are high level approximations only; given the small size of the population treated each year, these figures may vary. These figures combine two cohorts, those that start ITI for the first 12 months and those that complete ITI for the remaining 4 months.

[xv] Based on discussions with the policy working group.

[xvi] Based on discussions with the policy working group, successful patients (i.e. patients that tolerate administered FVII after ITI) would receive prophylactic treatment with FEIBA in future years indefinitely. The dosages for such patients vary and range from 50 units per kg of body weight every other day to 100 units per kg daily. Based on an average body weight of 10kg-20kg, the usage of FEIBA per patient for prophylaxis could range from 90,000 to 720,000 units per year.

[xvii] Based on discussions with the policy working group.

[xviii] UKHCDO. UK National Haemophilia Database Bleeding Disorder Statistics for 2013-14 for children with severe haemophilia A and no current inhibitor. Excludes outliers.

[xix] The most frequently used bypassing agents within the NHS are: *FEIBA* and *NovoSeven* (based on policy proposition and discussions with the policy working group).

[xx] Based on discussions with the policy working group.

[xxi] Based on discussions with the policy working group, patients with inhibitors could receive prophylactic treatment with FEIBA in future years indefinitely. The dosages for such patients vary and range from 50 units per kg of body weight every other day to 100 units per kg daily, however dosages could even be higher [Source: policy working group discussions; the electronic Medicines Compendium (eMC)*. FEIBA 1000 U powder and solvent for solution for infusion.* [Online] Available from: http://www.medicines.org.uk/emc/medicine/30168 [accessed: 04.02/2016].]. Based on an average body weight of 80kg-90kg, the usage of FEIBA per patient for prophylaxis could range from at least 720,000 to 3,240,000 units in a year.

[xxii] Based on discussions with the policy working group. Around 400 haemophiliacs in the UK were infected with HIV after receiving infected blood for treatment in the late 1970s and 1980s. [Source: Terrence Higgins Trust (2014). *Haemophilia and HIV*. [Online] Available from http://www.tht.org.uk/myhiv/HIV-and-you/Your-diagnosis/Haemophilia-and-HIV [Accessed: 10/12/2015]. The high mortality associated with HIV and hepatitis [Source: Public Health England (2013). "HIV in the United Kingdom: 2013 Report"; and Public Health England (2014). "Hepatitis C in the UK: 2014 report"] thus affects the prevalence of haemophilia A.

[xxiii] This applies the growth rate described to the prevalence outlined in K1.1.

[xxiv] UKHCDO. UK National Haemophilia Database Bleeding Disorder Statistics for 2008-2009, 2009-2010, 2010-2011, 2011-2012, 2012-2013, 2013-2014.

[xxv] This applies the growth rate described to the target population outlined in K1.2.

[xxvi] This applies the estimated population growth rate for the male population aged 18 and above to the number identified in K1.1 [Source: ONS (2012). Population Projections].

[xxvii] Based on discussions with the policy working group. There may also be patients that develop inhibitors to Factor VIII later in life, which have not been included in this estimate as the appropriateness for that group would be unclear.

[xxviii] Based on the c. 2 adult patients per year newly diagnosed adult patients with severe haemophilia A that are estimated to have inhibitors (as set out in K1.2). Applying the growth rate of net migration [Based on ONS (2012). Population projections] results in c 2 patients in 2014/15.

[xxix] Based on the stylised pathway outlined in endnote xiv.

[xxx] Source: UKHCDO. UK National Haemophilia Database Bleeding Disorder Statistics for 2013-2014. As more granular data was not available, this includes patients with no current factor VIII inhibitor. No evidence of differences in the proportion of all patients with severe haemophilia A that are children or that develop factor VIII inhibitors was identified.

[xxxi] NHS Choices (2015). *Haemophilia – Causes*. [Online] Available from: http://www.nhs.uk/Conditions/Haemophilia/Pages/causes.aspx [Accessed: 19/11/2015].

[xxxii] Based on discussions with the policy working group.

[xxxiii] Based on discussions with the policy working group.

[xxxiv] Based on discussions with the policy working group and the policy documentation.

[xxxv] Based on the cost for *ReFacto* 250unit powder and solvent for solution for injection vials (Wyeth Pharmaceuticals) 1 vial, and *Advate* 250unit powder and solvent for solution for injection vials (Baxter Healthcare Ltd) 1 vial. Please refer to: http://dmd.medicines.org.uk/. These products were defined in discussions with the policy working group.

[xxxvi] Based on correspondence the policy working group.

[xxxvii] *Section 3.2, When can goods being provided on prescription be zero-rated for VAT purposes?* https://www.gov.uk/government/publications/vat-notice-70157-health-professionals-and-pharmaceutical-products/vat-notice-70157-health-professionals-and-pharmaceutical-products

[xxxviii] Based on an average weight per patients between 10kg and 20kg and the pathway described in endnote xiv. The units required therefore range from 50/kg every other day to 200/kg daily. An average cost per 250 units of FVIII of c.£150 is used (average of £126 and £178 described in M1.3). Moreover, homecare delivery costs in the region of £600 to £3,600 per patient are estimated (Based on 6-12 deliveries per year and a cost of £50 100 to £100 300 per delivery [based on discussions with NHS England public health lead and the policy working group]).Other costs associated with administering FVIII for ITI were not considered as they are minimal compared to the cost of the treatment itself (based on discussions with the policy working group).

[xxxix] For example, there could be on 6-12 deliveries per year and a cost of £100 to £300 per delivery (based on discussions with NHS England public health lead), in comparison to the drug cost of over £100,000.

[xl] Based on discussions with the policy working group. There is however some variation in the length of treatment across patients.

[xli] Following the approach outlined in endnotes xiv and xl.

[xlii] Based on the average dosage per patient per year during the tapering phase of 220,000 to 430,000 units of FVIII. This calculation takes the average between the typical number of units per patient per year after successful ITI (100,000 – 200,000 based on discussion with the policy working group) and the number of units during ITI.

[xliii] Based on 20 to 50 units per kg of body weight every other day, an average weight of 10kg to 20kg for children and 80kg to 90kg for adults and an average cost of £150 per 250 units of FVIII.

[xliv] Based on 50 units per kg of body weight every other day to 100 units per kg daily, an average weight of 10kg to 20kg for children, an average weight of 80kg to 90kg for adults and an average cost of £780 per 1,000 units of FEIBA (a bypassing agent) [Source: Baxter Healthcare. FEIBA (Factor Eight Inhibitor Bypassing Activity) - Prescribing information. [Online] Available from http://www.baxterhealthcare.co.uk/downloads/prescribing_information/biopharma/feiba_pi_uk_july_2014.pdf [Accessed: 14/12/2015]].